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Patents, Trademarks, Designs, Licences

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European Patent Office
D-80298 Munich

26 July 2004

Re: International Patent Application No. PCT/EP 03/09746
Applicant: VitaK BV
Our ref.: 03/116 PCT

Dear Sirs,

Reference is made to the Written Opinion dated 26.04.2004.

We have noted that the originally filed claims 1, 2, 4, 5, 8, 13, 17, 18, 19 are considered not novel in view of documents D1, D2, D5, D6 and D7, that claim 18 as presently worded is considered not unitary with the subject-matter of claims 1-17 and 19 of the present application, that claim 19 is considered not to involve an inventive step under the provisions of the EPC, and that dependent claims 3, 6, 7, 9-12 and 14-16 as such do not involve an inventive step.

The present invention relates to the effect of vitamin K on vascular stiffening. See, *inter alia*, p.2, l.22 ff.: "Vascular stiffening is due to the loss of elasticity of arteries. Vascular stiffening is associated with aging, diabetes mellitus and renal dysfunction; it is the result of degradation of the elastic lamellae in the tunica media resulting in loss of elasticity".

Vascular stiffening is the degradation of elastin, due to the enzyme elastase, and is characterized by a decrease of the elastin / collagen ratio. Because of the loss of elastin, the elastic properties of the vasculature become dependent of collagen, which is far more rigid. Hence the vessels become stiff.

As reviewed by Oxenham and Sharpe (Oxenham, H. and Sharpe, N.: *Cardiovascular aging and heart failure*. *Eur. J. Heart Failure* 5 (2003) 427-434, copy enclosed), "increasing age is associated with increased fragmentation of the internal elastic membrane and an increase in the amount of collagen in arterial walls. A progressive arterial dilatation as well as increased arterial thickening and stiffness accompany these microscopic changes. Arterial stiffening is associated with aging in Western societies even in the absence of demonstrable cardiovascular disease. It manifests itself as increased systolic blood pressure, widening of the pulse pressure and increased wave velocity."

In contrast, arteriosclerosis stands for vascular disease, although various authors give different definitions. According to the most broad definition, it may be split up into:

- Vascular media calcification (also called vascular 'hardening' or 'Mönckeberg's sclerosis'), which comprises accumulation of calcium salts in the tunica media. The disease mainly manifests itself in diabetes mellitus and end-stage renal disease, but to some extent it is also regarded as a complication of aging.

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For a review, see also: Shanahan, C.M., Cary, N.R.B., Salisbury, J.R., Proudfoot, D., Weissberg, P.L., Edmonds, M.E. *Medial localization of mineralization-regulating proteins in association with Mönckeberg's sclerosis*. *Circulation* 100 (1999) 2168-2176 (copy enclosed).

- Atherosclerosis, a typical disease of the arterial intima, is associated with inflammation, macrophage infiltration, foam cell and plaque formation and in more advanced stages also with calcification. For a review, see Rosenfeld, M.E., *An overview of the evolution of the atherosclerotic plaque: from fatty streak to plaque rupture and thrombosis*. *Z. Kardiol* 89: Suppl 7 VII/2-VII/6 (2000) (copy enclosed).

Hence both Mönckeberg's sclerosis and atherosclerosis are two forms of vascular disease, whereas vascular stiffening is found in health and disease. Stiffening itself is NOT a disease, but it is a risk factor for the development of vascular disease. In a comparable way high blood cholesterol and high blood sugar are risk factors for the development of cardiovascular disease. Therefore, the reduction of the process of elastin degradation leading to a decreased rate of vascular stiffening is not a treatment of cardiovascular disease, but the elimination of a risk factor.

The Examiner cited D3 and D4 in support of the common general knowledge regarding the term "arteriosclerosis". While D4 indicates that it is almost impossible to define "arteriosclerosis" in one sentence, it will be clear that the one sentence "summary" rather than a definition given in D3 ("a generic term for several diseases in which the arterial wall becomes thickened and loses elasticity") is far too broad and should be read in the context of the whole reference.

Therefore, the present invention relates to a new medical use of vitamin K which is distinct from earlier uses of vitamin K. As explained above, arterial stiffening is a general problem in aging. Certain diseases, such as diabetes mellitus and renal dysfunction, are associated with increased or accelerated arterial stiffening. As will be clear from the patent specification, supplementation of vitamin K to an individual is not to cure these diseases, but to prevent complications which are associated with cardiovascular disorders. It is emphasized, however, that the prior art does not teach or suggest the beneficial action of vitamin K on arterial stiffening which is the object of the present invention.

We herewith file a new set of claims, for the purpose of this preliminary examination, which is believed to better define the present invention and to distinguish it from the cited prior art.

As compared to the originally filed set of claims, claim 1 has been amended by adding the phrase "not associated with arteriosclerosis" for reasons indicated above. The formal basis for this amendment can be found throughout the specification. Original claims 2 to 4 have been deleted. Original dependent claims 5 to 12 have been renumbered as claims 2 to 9 and the referrals to previous claims has been adapted. Original composition claims 13-17 have been rewritten as use claims and linked to the previous use claims. Original claim 18 has been cancelled, and claim 19 has been restricted in conformity with the previous claims (in particular claim 1) and renumbered as 15. No new matter has been introduced.

As stated above, the subject-matter of independent claims 1 and 15 is believed to be new and inventive, since none of the cited references disclose or suggest the use of vitamin K or a derivative thereof in treating or preventing age-related stiffening of arteries which is not associated with arteriosclerosis. Dependent claims 2 to 14 which

are all directly or indirectly dependent on claim 1 define certain preferred embodiments of the present invention.

Since the Applicant is eager to receive a positive International Preliminary Examination Report, the Examiner is kindly requested to contact the undersigned by telephone to discuss possible remaining objections and to give another opportunity to amend the claims and/or specification before issuing the IPER.

Please acknowledge receipt of these documents by returning the enclosed copy of this letter (to be sent with the confirmation letter of this fax), duly endorsed.

Yours faithfully,

Arthur V. Huygens
Authorised Representative

Encl.: new set of claims (triplicate)
three references (with confirmation copy only)
copy of this letter to acknowledge receipt (with confirmation copy only)

Proposed New Claims

(26-07-2004)

5 1. Use of a composition comprising vitamin K or a derivative thereof, optionally together with vitamin D or a derivative thereof, in the manufacture of a medicament or nutritional formulation for treating or preventing age-related stiffening of arteries not associated with arteriosclerosis.

10 2. Use of a composition comprising vitamin K or a derivative thereof, optionally together with vitamin D or a derivative thereof, in the manufacture of a medicament or nutritional formulation for treating or preventing an age-related decrease in compliance and/or distensibility of arteries and/or an age-related increase in pulse pressure.

15 3. Use of a composition according to claim 1 wherein said artery stiffening results from calcification of the tunica media.

20 4. Use of a composition comprising vitamin K or a derivative thereof, optionally together with vitamin D or a derivative thereof, in the manufacture of a medicament or nutritional formulation for treating or preventing any of: hypertension, left ventricular hypertrophy, congestive heart failure, myocardial infarction, stroke, Mönckeberg's sclerosis and coronary heart disease.

25 25. Use of a composition according to any of claims 1 to 4, wherein said vitamin K is vitamin K₁ (phylloquinone) or vitamin K₂ (menaquinone).

30 36. Use of a composition according to claim 25 wherein said vitamin K is vitamin K₁ (phylloquinone).

35 47. Use of a composition according to any one of claims 1 to 36 wherein the daily dosage of vitamin K or a derivative thereof is in the range 50µg-1000µg.

58. Use of a composition according to any one of claims 1 to 47
wherein the medicament or nutritional composition comprises vitamin D or a derivative
thereof.

5 69. Use of a composition according to claim 58 wherein said vitamin D
is vitamin D₃ (cholecalciferol).

740. Use of a composition according to any of claims 1 to 69 wherein
the medicament or nutritional formulation is for administration to a postmenopausal
10 woman.

841. Use of a composition according to any of claims 1 to 740 wherein
the medicament or nutritional formulation is to be administered over a period of at least
12 months, preferably at least 36 months.

15 942. Use of a composition according to claim 1 or claim 2 wherein said
arteries are the common carotid arteries.

1043. Use of aA composition according to any one of claims 1-9 for
20 promoting healthy arteries, comprising:

(a) vitamin K or a derivative thereof, and optionally together with vitamin D or
a derivative thereof, further comprising
(b) one or more additional components selected from: polyphenols, vitamin
C, vitamin E (tocopherols and/or tocotrienols), L-Arginine, phytosterols, antihypertensive
25 peptides, soluble fibers (e.g. guar, pectin), omega-3, omega-6 and/or omega-9 fatty
acids, carnitine, taurine, coenzyme Q10, creatine, folic acid, folates, magnesium,
potassium, vitamin B6, and vitamin B12, and
(c) optionally, vitamin D or a derivative thereof.

30 1144. Use of aA composition according to claim 1043 which comprises in
a single dose: 0.5-1mg vitamin K and 5-10 μ g vitamin D.

1245. Use of aA composition according to claim 10 for promoting healthy
arteries which comprises: 0.5-1.5mg vitamin K; 5-10 μ g vitamin D; 450-550mg Calcium;
35 7-12 mg Zinc; and 100-200mg Magnesium.

1316. Use of aA composition according to claim 1245 which comprises about 1mg Vitamin K₁; 8 µg vitamin D₃, 500mg Calcium, 10mg Zinc; and 150mg Magnesium.

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1417. Use of aA composition according to any of claims 1043 to 1316 which is a food or beverage product or a dietary supplement.

18. A kit comprising Vitamin K or a derivative thereof, and optionally vitamin D or a derivative thereof, and a medicament, for simultaneous, separate or sequential administration, wherein said medicament is selected from the group consisting of: anticoagulants, antithrombotics, fibrinolytics, antihypertensives, diuretics, antianginals, hypolipidaemic agents, beta-blockers, ACE inhibitors, cardiac glycosides, phosphodiesterase inhibitors, antiarrhythmics, and calcium antagonists.

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1549. A method of preventing or treating age-related arterial stiffening, hypertension, left ventricular hypertrophy, congestive heart failure, myocardial infarction, stroke, Mönckeberg's sclerosis or coronary heart disease, not associated with arteriosclerosis, comprising administering to a person in need of such treatment an effective amount of vitamin K or a derivative thereof and optionally vitamin D or a derivative thereof.

Hr. Vermeer: ik heb de neiging om ons in dit stadium helemaal te concentreren op claim 1 en met name claim 2 en 3 te schrappen. Het lijkt mij dat de Examiner moeite zal hebben om goede literatuur tegen claim 1 te vinden, terwijl wij veel gemakkelijker gepakt kunnen worden op claim 2 of 3. De redenering van de Examiner zou kunnen zijn: het doet er niet toe of een werking al of niet geassocieerd is met arteriosclerose; zolang de vitamine K in verband wordt gebracht de behandeling (of preventie) van een bepaalde ziekte of stoornis is de zaak niet meer nieuw, wat ook het mechanisme is. Wat vindt u?

Proposed New Claims

(26-07-2004)

5 1. Use of a composition comprising vitamin K or a derivative thereof, optionally together with vitamin D or a derivative thereof, in the manufacture of a medicament or nutritional formulation for treating or preventing age-related stiffening of arteries, not associated with arteriosclerosis.

10 2. Use of a composition according to claim 1, wherein said vitamin K is vitamin K₁ (phylloquinone) or vitamin K₂ (menaquinone).

15 3. Use of a composition according to claim 2 wherein said vitamin K is vitamin K₁ (phylloquinone).

15 4. Use of a composition according to any one of claims 1 to 3 wherein the daily dosage of vitamin K or a derivative thereof is in the range 50μg-1000μg.

20 5. Use of a composition according to any one of claims 1 to 4 wherein the medicament or nutritional composition comprises vitamin D or a derivative thereof.

20 6. Use of a composition according to claim 5 wherein said vitamin D is vitamin D₃ (cholecalciferol).

25 7. Use of a composition according to any of claims 1 to 6 wherein the medicament or nutritional formulation is for administration to a postmenopausal woman.

30 8. Use of a composition according to any of claims 1 to 7 wherein the medicament or nutritional formulation is to be administered over a period of at least 12 months, preferably at least 36 months.

35 9. Use of a composition according to claim 1 wherein said arteries are the common carotid arteries.

35 10. Use of a composition according to any one of claims 1-9 for promoting healthy arteries, comprising vitamin K or a derivative thereof, optionally together with

vitamin D or a derivative thereof, further comprising one or more additional components selected from: polyphenols, vitamin C, vitamin E (tocopherols and/or tocotrienols), L-arginine, phytosterols, antihypertensive peptides, soluble fibers (e.g. guar, pectin), omega-3, omega-6 and/or omega-9 fatty acids, carnitine, taurine, coenzyme Q10, 5 creatine, folic acid, folates, magnesium, potassium, vitamin B6, and vitamin B12.

11. Use of a composition according to claim 10 which comprises in a single dose: 0.5-1mg vitamin K and 5-10 μ g vitamin D.

10 12. Use of a composition according to claim 10 which comprises: 0.5-1.5mg vitamin K; 5-10 μ g vitamin D; 450-550mg Calcium; 7-12 mg Zinc; and 100-200mg Magnesium.

13. Use of a composition according to claim 12 which comprises about 1mg 15 Vitamin K₁; 8 μ g vitamin D₃, 500mg Calcium, 10mg Zinc; and 150mg Magnesium.

14. Use of a composition according to any of claims 10 to 13 which is a food or beverage product or a dietary supplement.

20 15. A method of preventing or treating age-related arterial stiffening, not associated with arteriosclerosis, comprising administering to a person in need of such treatment an effective amount of vitamin K or a derivative thereof and optionally vitamin D or a derivative thereof.